Centers for Education & Research on Therapeutics

a program of the Agency for Healthcare Research and Quality

July 6, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment; Docket No. 2004D-0189.

The Centers for Education & Research on Therapeutics (CERTs) appreciate the opportunity to comment on the draft Guidance related to pharmacovigilance and pharmacoepidemiology. The CERTs demonstration program is a national initiative to conduct research and provide education that advances the optimal use of drugs, medical devices, and biological products. The program, authorized by Congress as part of the FDAMA 1997, is administered and funded as a cooperative agreement by the Agency for Healthcare Research & Quality (AHRQ), in consultation with the Food and Drug Administration (FDA). Seven centers (each with a particular population focus), a Coordinating Center, a Steering Committee, and numerous partnerships with public and private organizations make up the CERTs program. Over 200 research and education projects are included in the CERTs portfolio.

Risk management is a critical topic to advance the optimal use of therapeutics. One CERTs initiative aimed at addressing risk management was the organization of a series of "think tank" workshops to identify priority research issues that could improve the nation's ability to assess, communicate, and manage therapeutic risk called the Risk Series. The priority research issues resulting from the Risk Series were announced in March 2003 (see http://www.certs.hhs.gov/programs/risk_series/index.html).

Based on the issues identified in the Risk Series, as well as the expertise and work of CERTs investigators, below are some comments and suggestions related to the draft Guidance.

Section III. The Role of Pharmacovigilance in Risk Management

The definition of pharmacovigilance (lines 115-119) seems unconventional. Most people use the term pharmacovigilance roughly to mean what one does with spontaneous reports, and pharmacoepidemiology to mean formal studies. Pharmacoepidemiology is

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not a subset of pharmacovigilance. The Guidance indicates that good pharmacovigilance practice is "generally based" on acquiring complete data from spontaneous reports and developing a case series. This description makes sense only if pharmacovigilance is defined in the more traditional sense. We suggest the FDA consider changing the name of Section III to "The Role of Pharmacovigilance and Pharmacoepidemiology in Risk Management," and define pharmacoepidemiology.

Section IV. Identifying and Describing Safety Signals: From Case Reports to Case Series

The Guidance indicates that good case reports should include information about concomitant product therapy details. We recommend that FDA clarify this element to make it clear that concomitant products include over-the-counter medications and dietary supplements. Information regarding recently discontinued medications that may have longer half-lives or medications that have lasting effects after drug withdrawal should also be recorded in case reports. We recommend that similar clarifications be made in the list of elements analyzed in a case series.

On the topic of assigning causality to a safety signal, the Agency indicates no preference for a particular categorization system. However, if a causality assessment is undertaken, "FDA suggests that the causal categories are specified." We recommend the statement be expanded, i.e., "FDA suggests that the causal categories are specified and described in sufficient detail to determine the underlying logic in the classification, and how the classification corresponds to other classification systems for assigning causality in signals."

Suggested new statement. Premarketing risk assessment may include toxicity data not confirmed in clinical trial data, but which still suggest a significant safety concern for a marketed drug. In such cases both the expected incidence of the adverse event and the expected frequency of exposure to the drug may also be extremely small. In these circumstances, standard observational methods of signal detection such as spontaneous reporting and case-control studies may not be sufficient to detect signals. The agency should recognize the need for innovation in methods of pharmacovigilance, and encourage sponsors, researchers, and collaborating institutions to explore innovative approaches to collect and analyze postmarketing signals. Included in this is a concern for the effects of HIPAA in reducing participation by health care provider organizations. FDA encourages researchers and collaborating organizations to explore all options in developing collaborations and methodologies that will help answer questions of low incidence and low exposure conditions, while assuring confidentiality and privacy in patient records.

With regard to data mining, the Guidance in one place indicates that data mining is a technique used to make causal attributions between products and adverse events (lines 316-317), and in other places that data mining may be useful for generating signals but not for testing hypotheses. We believe that only the latter is correct. Also, the term "data mining" can be used to describe activities beyond what is referenced in the Guidance, such as neural networks, for example, which are attempts to look for patterns which

otherwise would not be seen. Using such experimental approaches on unstructured data is fraught with risk, especially in a regulatory process that is filled with litigation. Further, FDA should make clearer that this is a purely experimental approach, with no evidence that it works any better than reviews of single cases. Indeed, there are reasons to think the latter are better, as people over-interpret anything quantitative. Additional research on this approach would be critical, before it is set in stone in regulation.

In order to improve the flow of the document, we suggest the order of Section VI (Interpreting Safety Signals: From Signal to Potential Safety Risk) and Section V (Beyond Case Review: Investigating a Signal Through Observational Studies) be switched since Section VI discusses what to do when a signal has been identified, including the potential for following up with controlled pharmacoepidemiologic studies, and Section V discusses those studies.

Section V. Beyond Case Review: Investigating a Signal through Observational Studies

The Guidance suggests that pharmacoepidemiologic safety studies, registries, and surveys are different, while most would consider the latter two pharmacoepidemiologic studies also. These distinctions are not clear. Also, the wording suggests that large simple safety studies (LSSS) are acceptable when relevant, but since they are covered in the premarketing document, this suggests they are not centrally important postmarketing. The wording in this Guidance could be stronger, e.g., explicitly listing it within the pharmacoepidemiology options, before referring the reader to the other document.

The Guidance indicates that pharmacoepidemiologic safety studies are nonrandomized observational studies, but in fact pharmacoepidemiologic safety studies can be either randomized or non-randomized. Therefore, we suggest that the word "nonrandomized" be deleted.

Registries are an approach to signal evaluation indicated in the Guidance document. However, it is not clear how a registry, as described, differs from an ad hoc cohort study in pharmacoepidemiology. Further, the use of registries, without control groups, raises numerous interpretation issues. In addition, and critically, we suggest that the final document specify that recruitment into registries must be systematic. While this is not commonly done in pharmacoepidemiology, it is mandatory in the rest of epidemiology, and without systematic complete collection of all cases fitting the specified definition, registries are prone to yielding biased, misleading results.

Section VII. Beyond Routine Pharmacovigilance: Developing a Pharmacovigilance Plan

We suggest that FDA clarify the electronic health information system adverse event collection mechanism referenced in the Guidance. The current language seems to imply that such health information systems are useful for generating spontaneous reports. However, we agree with the concept that approaches need to be compatible with the increasing use of electronic health information systems.

We appreciate the opportunity to provide suggestions for a document that will provide important guidance to industry about the identification, assessment and management of therapeutic risks.

Sincerely,

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